

REMARKS

A Petition for Extension of Time is being concurrently filed with this Amendment. Thus, this Amendment is being timely filed.

Applicants respectfully request the Examiner to reconsider the present application in view of the foregoing amendments to the claims and the following remarks.

Status of the Claims

Claims 1, 3 and 4 are currently pending in the present application. Claims 2 and 5 have been cancelled without prejudice or disclaimer. Claim 1 is amended, without prejudice or disclaimer, to include "isolated" within the claim. Support for amended claim 1 can be found on page 2, lines 14-25 of the present specification. Thus, no new matter has been added.

Based upon the above considerations, entry of the present Amendment is respectfully requested.

English Translation of Priority Application

Applicants desire to obtain benefit of foreign priority under 35 U.S.C. § 119(a). Enclosed herewith is a certified English translation of the Japanese Patent Application No. 2002-244280, filed August 23, 2002. The same provides full 35 U.S.C. § 112 support for the invention as instantly claimed.

Applicants respectfully request consideration and subsequent admission of the above English translation.

Objection to the Specification

The Examiner states that the title of the invention is not descriptive. Applicants have amended the title to "Human Bone Stem Cells From Amniotic Mesenchymal Cell Layer" as the Examiner suggested. Applicants respectfully request reconsideration and withdrawal of the present objection.

Issue Under 35 U.S.C. § 112, Second Paragraph, Indefiniteness

Claims 2-5 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Applicants have cancelled claims 2 and 5, without prejudice or disclaimer, thus obviating the rejection as to these claims.

The Examiner asserts that claims 2-5 disclose the limitation "bone stem cells existing in human amniotic mesenchymal cell layer," and it is not clear to the Examiner as to what this limitation intends to claim. The Examiner asserts that the limitation of "bone stem cells existing in human amniotic mesenchymal cell layer" can be interpreted as bone stem cells isolated from human amniotic mesenchymal cell layer or bone stem cells that are physically present in the human amniotic mesenchymal cell layer without isolation. Applicants respectfully traverse as to remaining claims 1, 3 and 4.

Applicants respectfully submit that any terms or phrases *per se* in the rejected claims are clear, so that the alleged vagueness is created by the Examiner. Since there is no limitation in remaining claims 1, 3 and 4 whether the "bone stem cells existing in human amniotic

mesenchymal cell layer” are isolated stem cells or cells physically present in the human amniotic mesenchymal cell layer without isolation, it is apparent that the claims include both cases where the cells are isolated and where the cells are physically present in the human amniotic mesenchymal cell layer without isolation. Additionally, since claims 3 and 4 are method claims, it is apparent to one in the art that obtaining bone cells which are from culturing bone stem cells existing in human amniotic mesenchymal cell layer (claim 3) were isolated by the mere fact that they are in a cell culture. This is also evident in claim 4 since the method for osteogenesis has to have bone stem cells existing in human amniotic mesenchymal cell layer for transplantation. Therefore, the remaining claims are not indefinite or vague, as the Examiner asserts. Applicants respectfully request reconsideration and withdrawal of the present rejection

Issue Under 35 U.S.C. § 101, Non-Statutory Subject Matter

Claims 2 and 5 stand rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter.

Applicants have cancelled claims 2 and 5, without prejudice or disclaimer, thus obviating the present rejection. Applicants respectfully request reconsideration and withdrawal of the present rejection.

Issues Under 35 U.S.C. § 102(b), Anticipation

The Examiner has cited the following 35 U.S.C. § 102(b) rejections below.

Claims 1-5 stand rejected under 35 U.S.C. § 102(b) as anticipated by Hung *et al.*, U.S. Patent Application Publication No. 2002/0045260 (hereinafter “Hung”), in light of Whittle *et al.*,

"The Characterization of Human Amnion Epithelial and Mesenchymal Cells: the Cellular Expression, Activity and Glucocorticoid Regulation of Prostaglandin Output," Placenta Vol. 21, pp. 394-401, (2000) (hereinafter "Whittle").

Claim 2 is rejected under 35 U.S.C. 102(b) as being anticipated by Whittle, in light of Nikaido, WO/2003/047607 (hereinafter "Nikaido"), and Alviano *et al.*, "*Term Amniotic Membrane is a High Throughput Source for Multipotent Mesenchymal Stem Cells with the Ability to Differentiate into Endothelial Cells In Vitro*," BMC Developmental Biology, Vol.7 (2007) (hereinafter "Alviano").

The above rejections are respectfully traversed.

Applicants have cancelled claims 2 and 5, without prejudice or disclaimer, thus obviating the rejections as to these claims.

With regards to the rejection concerning remaining claims 1, 3 and 4, the Examiner asserts that Hung teaches mesenchymal stem cells are capable of differentiating into bone cells obtainable from placenta, and a method of culturing mesenchymal stem cells in an osteogenic culture medium to differentiate the mesenchymal stem cells into osteoblasts. The Examiner also asserts that Hung teaches a method of tissue replacement (considered as transplantation) using mesenchymal stem cells and transplanting mesenchymal stem cells.

The Examiner additionally asserts that Hung discloses the source of human mesenchymal stem cells as the placenta. As evidenced in Whittle, the Examiner suggests that it is well known in the art that an amniotic mesenchymal cell layer is a part of amniotic membrane of a placenta, and that the mesenchymal stem cells derived from placenta are considered to encompass the

mesenchymal stem cells separated from the amniotic mesenchymal cell layer. Applicants respectfully disagree with the Examiner.

Hung discloses findings regarding the placenta. In contrast, the present invention is related to the isolated cell separated from amniotic mesenchymal cell layer. Therefore, Hung and the present invention are completely different.

As is expressly stated in the specification of the present application on page 2, lines 16-18, the placenta is originated from the mother while amnion is originated from the fetus. It is apparent for those skilled in the art that cells from an adult woman (mother) are different from the cells from the fetus. By virtue of the fact that the amnion is originated from the fetus, the cells of the present invention are immunologically tolerant, as expressly stated in the paragraph bridging pages 3 and 4 of the specification of the present application. This very advantageous feature is not obtained by using cells from placenta originated from the adult woman.

Since the teachings by Hung are limited to those concerning the placenta, Hung does not disclose the present invention.

With regards to Whittle, the Whittle reference discloses information about amnion and teaches that mesenchymal cells exist in the amnion.

However, Whittle is completely silent about the discovery that bone stem cells exist in the amniotic mesenchymal cell layer. On the other hand, as amended, claim 1 of the present invention claims an isolated bone stem cell. Since Whittle is silent about the discovery that bone stem cells exist in the amniotic mesenchymal cell layer, Whittle does not teach the amended claim 1 or any other claims in the present application.

Because “a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference,” the cited Hung or Whittle references cannot be a basis for a rejection under § 102(b). See *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Applicants respectfully request reconsideration and withdrawal of the present rejection.

Issue Under 35 U.S.C. § 102(a), Anticipation

Claims 1, 2 and 5 stand rejected under 35 U.S.C. § 102(a) as anticipated by Nikaido in light of Alviado.

Applicants have cancelled claims 2 and 5, without prejudice or disclaimer, thus obviating the rejection as to these claims. Applicants respectfully traverse the rejection as to claim 1.

The Nikaido reference published on June 12, 2003 and thus qualifies under 35 U.S.C. §102(a). Applicants note that since Nikaido published in Japanese, the PCT filing date of December 5, 2002 is not an effective date under 35 U.S.C. § 102(e). Regardless, since the present application claims priority to JP 2002-244280, filed August 23, 2002, by supplying herein the certified English translation of JP 2002-244280, the present application antedates the Nikaido reference. Thus, Nikaido cannot be used as a prior art reference against the present application.

With regards to Alviano, this reference was published in 2007, which is well after the international filing date of the present invention, such that Alviano cannot be used as a prior art reference against the present application.

Applicants respectfully request reconsideration and withdrawal of the present rejection.

Issue Under 35 U.S.C. § 103(a), Obviousness

Claims 1-5 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Hung, in view of Nikaido, or Whittle. Applicants traverse.

As a preliminary matter, as discussed above, since Applicants have enclosed the certified English translation of JP 2002-244280, Nikaido should be removed as prior art. Therefore, the asserted teaching of Nikaido by the Examiner (page 10, line 12, to page 11, line 7 of the present Office Action dated March 31, 2008) are no longer applicable. Additionally, the assertion by the Examiner on the motivations of the skilled artisan to make such a modification (or the expectation of success) using the Nikaido reference are no longer applicable as well.

Additionally, Applicants have cancelled claims 2 and 5, without prejudice or disclaimer, thus obviating the rejection as to these claims.

The Examiner also asserts that it would have been obvious to recognize that the mesenchymal stem cells derived from placenta are from amniotic mesenchymal cell layers and that a person of ordinary skill in the art would recognize that the mesenchymal stem cells isolated from placenta as taught by Hung are existing in and derived from mesenchymal cell layers of the human amniotic membrane. Applicants disagree.

Graham v. John Deere, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966), has provided the controlling framework for an obviousness analysis. A proper analysis under § 103(a) requires consideration of the four *Graham* factors of: determining the scope and content of the prior art; ascertaining the differences between the prior art and the claims that are at issue; resolving the level of ordinary skill in the pertinent art; and evaluating any evidence of secondary considerations (e.g., commercial success; unexpected results). 383 U.S. at 17, 148 USPQ at 467.

M.P.E.P. § 2143 sets forth the guidelines in determining obviousness. But before the Examiner can utilize these guidelines, the Examiner has to take into account the factual inquiries set forth in *Graham v. John Deere, supra*. To reject a claim based on the above mentioned guidelines, the Examiner must resolve the *Graham* factual inquiries. MPEP §2143.

If the Examiner resolves the *Graham* factual inquiries, then the Examiner has to provide some rationale for determining obviousness, wherein M.P.E.P. § 2143 sets forth the rationales that were established in *KSR Int'l Co. v Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007).

Applicants respectfully submit that the Examiner has not appropriately resolved the *Graham* factors, including the factors of determining the scope and content of the prior art and ascertaining the differences between the prior art and the claims that are at issue. Based on the following, Applicants maintain that the above mentioned *Graham* factors actually reside in Applicants' favor. Additionally, Applicants submit that since the Examiner did not resolve the *Graham* factors, the rationale the Examiner provides for combining the cited references is improper.

Applicants respectfully submit that the present invention is distinct from the cited references Hung and Whittle as discussed above in the previous rejections and is hereby incorporated by reference.

The courts since *KSR Int'l Co. v Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007), have recognized that inventors face additional barriers in relatively unpredictable technological areas as noted in *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd., supra* (since TSM test can provide helpful insight if it is not applied as rigid and mandatory formula, and since, in cases involving new chemical compounds, it remains necessary to identify some reason that would

have led chemist to modify known compound, in particular manner, in order to establish *prima facie* obviousness of new compound). This is also applicable to the biochemical arts. The cited references need to identify some reason that would have led a biochemist/biologist to modify the cited references, in particular manner, in order to establish *prima facie* obviousness of the present invention.

Based on the above-described differences of the present invention and the cited references, those skilled in the art would not recognize that Hung or Whittle teach or suggest the present invention.

Thus, it can be concluded that the Hung and Whittle reference do not disclose or suggest the surprising discovery made by the present inventors. As is expressly stated in the specification of the present application on page 2, lines 16-18, placenta is originated from the mother while amnion is originated from the fetus. It is apparent for those skilled in the art that cells from an adult woman (mother) are different from the cells from the fetus. By virtue of the fact that the amnion is originated from the fetus, the cells of the present invention are immunologically tolerant, as expressly stated in the paragraph bridging pages 3 and 4 of the specification of the present application. This very advantageous feature is not obtained by using cells from placenta originated from the adult woman.

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In light of the above remarks, because there is no disclosure, teaching, suggestion, reason or rationale provided in the cited references that would allow one of ordinary skill in the art to arrive at the instant invention as claimed, it follows that the same references are incapable of rendering the instant invention obvious under the provisions of 35 USC § 103(a). Based upon the above, and applying the *Graham factors* analysis test, it is submitted that a *prima facie* case of obviousness has not been established. “[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” *KSR*, quoting *In re Kahn*, 441 F.3d 977, 988 (CAFC 2006). Therefore, in light of the above, it is submitted that the Examiner did not meet the standard for a *prima facie* case of obviousness. Applicant respectfully requests reconsideration and subsequent withdrawal of the above rejections.

In view of the above remarks, Applicant believes the pending application is in condition for allowance.

CONCLUSION

A full and complete response has been made to all issues as cited in the Office Action. Applicants have taken substantial steps in efforts to advance prosecution of the present application. Thus, Applicants respectfully request that a timely Notice of Allowance issue for the present case.


In view of the above remarks, it is believed that claims are allowable.

Should there be any outstanding matters within the present application that need to be resolved, the Examiner is respectfully requested to contact Paul D. Pyla, Reg. No. 59,228, at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

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Respectfully submitted,

By 

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